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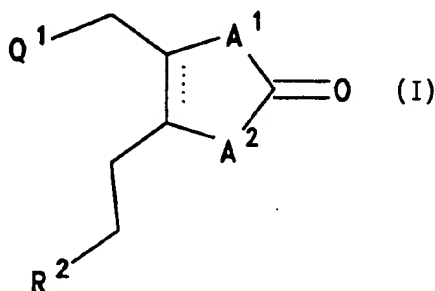
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(54) Title: IMIDAZOLINONE AND OXAZOLINONE DERIVATIVES AS TACHYKININ RECEPTOR ANTAGONISTS



(57) Abstract

Compounds of formula (I) and salts and prodrugs wherein Q¹ is a specified aryl group, the dotted line is an optional double bond, Z is O or NR³, R¹ and R³ are H or specified optionally substituted alkyl or other substituents and R² is an optionally substituted phenyl or group are tachykinin receptor antagonists useful in medicine.

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- 1 -

Imidazolinone and oxazolinone derivatives as tachykinin receptor antagonists.

This invention relates to a class of
5 heterocyclic compounds, in particular imidazolinone and
oxazolinone derivatives, which are useful as tachykinin
receptor antagonists.

The tachykinins are a group of naturally-
occurring peptides found widely distributed throughout
10 mammalian tissues, both within the central nervous system
and in the peripheral nervous and circulatory systems.
The three known mammalian tachykinins are:
substance P, neurokinin A and neurokinin B:

Evidence for the usefulness of tachykinin
15 receptor antagonists in pain, headache, especially
migraine, Alzheimer's disease, multiple sclerosis,
attenuation of morphine withdrawal, cardiovascular
changes, oedema, such as oedema caused by thermal injury,
chronic inflammatory diseases such as rheumatoid
20 arthritis, asthma/bronchial hyperreactivity and other
respiratory diseases including allergic rhinitis,
inflammatory diseases of the gut including ulcerative
colitis and Crohn disease, ocular injury and ocular
inflammatory diseases, proliferative vitreoretinopathy,
25 irritable bowel syndrome and disorders of bladder
function including cystitis and bladder detrusor hyper-
reflexia is reviewed in "Tachykinin Receptors and
Tachykinin Receptor Antagonists", C.A. Maggi, R.
Patacchini, P. Rovero and A. Giachetti, J. Auton.
30 Pharmacol. (1993) 13, 23-93. Tachykinin antagonists are
also believed to be useful in allergic conditions
[Hamelet et al Can. J. Pharmacol. Physiol. (1988) 66
1361-7], immunoregulation [Lotz et al Science (1988) 241
1218-21 and Kimball et al, J. Immunol. (1988) 141 (10)]

- 2 -

3564-9], and as anticonvulsants [Garant et al., Brain Research (1986) 382 372-8]. Tachykinin antagonists may also be useful in the treatment of small cell carcinomas, in particular small cell lung cancer (SCLC) [Langdon et al., Cancer Research (1992) 52, 4554-7].

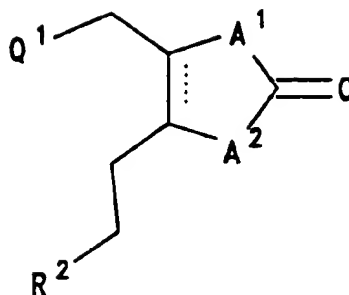
It has furthermore been suggested that tachykinins have utility in the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophillic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythmatosis (European patent application no. 0 436 334), conjunctivitis, vernal conjunctivitis, contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis (European patent application no. 0 394 989) and emesis (European patent application no. 0 533 280).

We have now found a class of non-peptides which are potent antagonists of tachykinins.

The present invention provides a compound of formula (I), or a salt or prodrug thereof:

30

- 3 -



(1)

wherein

Q^1 represents a phenyl group substituted by one or more halo, optionally substituted naphthyl, optionally substituted indolyl, optionally substituted benzthiophenyl, optionally substituted benzofuranyl, optionally substituted benzyl or optionally substituted fluorenyl;

the dotted line represents an optional covalent bond;

one of A^1 and A^2 represents NR^1 and the other is Z where Z represents O or NR^3 ;

R^1 and R^3 each independently represent H;

C_{1-6} alkyl optionally substituted by hydroxy, cyano, COR^C , CO_2R^C , $CONR^C R^d$, or $NR^C R^d$ (where R^C and R^d each independently represent H, C_{1-6} alkyl or C_{0-4} alkylphenyl optionally substituted in the phenyl ring by one or more of C_{1-6} alkyl, C_{1-6} alkoxy, halo or trifluoromethylmethyl); phenyl(C_{1-4} alkyl) (optionally substituted in the phenyl ring by one or more of C_{1-6} alkyl, C_{1-6} alkoxy, halo and trifluoromethyl); COR^C ; CO_2R^C ; $CONR^C R^d$; COC_{1-4} alkyl $NR^C R^d$; $CONR^C COOR^d$; SO_2R^C , where R^C and R^d are as above defined; WR^6 or $CO-Y-W-R^6$ where R^6 is an optionally substituted aromatic or non-aromatic azacyclic or azabicyclic group, Y is a bond, O, S or NR^Y , where R^Y is H or C_{1-6} alkyl, and

- 4 -

W represents a bond or a saturated or unsaturated hydrocarbon chain of 1, 2, 3, 4, 5 or 6 carbon atoms;

R^2 represents phenyl optionally substituted by 1, 2, or 3 groups selected from C_1 -6alkyl, C_2 -6alkenyl, C_2 -6alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, OR^a , SR^a , SOR^a , NR^aR^b , NR^aCOR^b , $NR^aCO_2R^b$, CO_2R^a or $CONR^aR^b$, where R^a and R^b independently represent H, C_1 -6alkyl, phenyl or trifluoromethyl.

For the avoidance of doubt, when the covalent bond represented by the dotted line is present, the compounds of formula (I) contain an olefinic double bond.

Aptly, this invention provides a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

As used herein, the definition of each expression, when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

The alkyl, alkenyl and alkynyl groups referred to with respect to any of the above formulae may represent straight, branched or cyclic groups or combinations thereof. Thus, for example, suitable alkyl groups include methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and cycloalkyl-alkyl groups such as cyclopropylmethyl; suitable alkenyl groups include vinyl and allyl; and suitable alkynyl groups include propargyl.

The term "halo" as used herein includes fluoro, chloro, bromo and iodo, especially chloro and fluoro.

Where Q^1 represents optionally substituted fluorenyl, the group is linked through the bridgehead carbon atom, that is to say, C-9.

Where Q^1 represents optionally substituted naphthyl, indolyl, benzothiophenyl, benzofuranyl, benzyl

- 5 -

or fluorenyl, suitable substituents include C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^a, SOR^a, SO₂R^a, OR^a, NR^aR^b, NR^aCOR^b, NR^aCOOR^b, COOR^a or CONR^aR^b, where R^a and R^b are as above defined. One or more substituents may be present and each may be located at any available ring position, except, where Q¹ is optionally substituted indolyl, the nitrogen atom. Where Q¹ is optionally substituted indolyl, suitable nitrogen substituents include C₁₋₆alkyl, optionally substituted phenyl(C₁₋₄alkyl), COOR^a or CONR^aR^b, wherein R^a and R^b are as above defined.

Suitable values of the group Q¹ include 3,4-dichlorophenyl, 3-indolyl, 2-naphthyl, 3-naphthyl, 9-fluorenyl, benzyl, 3-benzothiophenyl and 3-benzofuranyl.

Preferably Q¹ is 3-indolyl, 3-benzothiophenyl or 3,4-dichlorophenyl, more preferably 3-indolyl.

The aromatic or non-aromatic azacycle or azabicyclo R⁶ may contain one or more additional heteroatoms selected from O and S, or groups NR⁷, where R⁷ is H or C₁₋₆alkyl, and may be unsubstituted or substituted. Suitable substituents include C₁₋₆alkyl, C₁₋₆alkoxy, oxo, SH, =S, halo, trifluoromethyl, NR^aR^b, NR^aCOR^b, CONR^aR^b, CO₂R^a and CH₂OR^a, where R^a and R^b are as previously defined.

When R⁶ represents an aromatic azacycle or azabicyclo, suitable values of R⁶ include imidazolyl, triazolyl, tetrazolyl, oxazolyl, thiazolyl, pyrrolyl, pyrazolyl, pyrazinyl, pyridyl, oxadiazolyl, thiadiazolyl, isoxazolyl, isothiazolyl, benzimidazolyl, benzoxazolyl and indolyl, preferably imidazolyl, such as 2,4-imidazolyl, or pyridyl such as 4-, 3- or 2-pyridyl.

When R⁶ represents a non-aromatic azacycle or azabicyclo, suitable values of R⁶ include morpholinyl,

- 6 -

piperdiny1, pyrrolidinyl, piperazinyl, methylpiperazinyl, azanorbornanyl, 3,4-pyridinecarboxamido, quinuclidinyl, and azabicyclo[3.2.2]nonyl, preferably morpholinyl, piperazinyl, methylpiperazinyl, piperidinyl,
 5 pyrrolidinyl, quinuclidinyl (azabicyclo[2.2.2] octanyl) or azabicyclo[3.2.2]nonyl.

A subgroup of compounds according to the invention is represented by compounds of formula (I) wherein R^1 and R^3 each independently represent H;
 10 C_{1-6} alkyl optionally substituted by hydroxy, cyano, COR^C , CO_2R^C , $CONR^C R^d$, or $NR^C R^d$ (where R^C and R^d are as previously defined); phenyl(C_{1-4} alkyl) (optionally substituted in the phenyl ring by one or more of C_{1-6} alkyl, C_{1-6} alkoxy, halo and trifluoromethyl); COR^C ;
 15 CO_2R^C ; $CONR^C R^d$; $COC_{1-4}alkylNR^C R^d$; $CONR^C COOR^d$; SO_2R^C ; $(CH_2)_q R^6$ or $CO(CH_2)_q R^6$ where R^6 is as previously defined and q is 0, 1, 2, 3, 4, 5 or 6.

Preferably the double bond is present.

Aptly, A^1 represents O. In one group of
 20 particularly apt compounds A^1 is NR^1 .

Preferably Z is NR^3 .

In one group of compounds according to the invention, R^3 is preferably H or C_{1-3} alkyl, such as methyl.

25 In a preferred group of compounds of formula (I), R^3 represents C_{1-6} alkyl substituted by $NR^C R^d$ where R^C and R^d preferably represent C_{1-6} alkyl, such as C_{1-4} alkyl, e.g. methyl, or Y-W- R^6 , where Y preferably represents a bond, W preferably represents a bond or
 30 C_{1-4} alkyl and R^6 is preferably pyridyl, especially 4-pyridyl, pyridinyl, such as 4-pyridinyl, or morpholinyl.

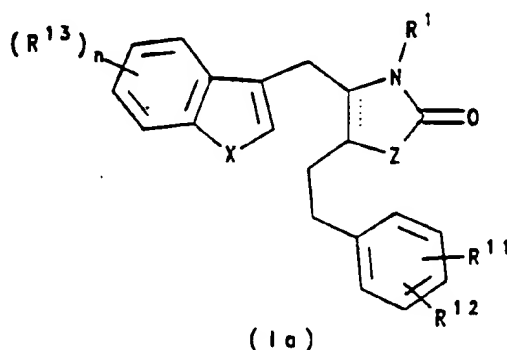
Preferably R^1 is H.

- 7 -

Preferably R^2 represents substituted phenyl. Suitable phenyl substituents include nitro, trifluoromethyl, trimethylsilyl, bromo, chloro, fluoro, iodo, cyano, methyl, ethyl, cyclopropyl, vinyl, methoxy, phenoxy and amino. Preferably R^2 represents monosubstituted or, more preferably, disubstituted phenyl wherein the substituents are selected from C_{1-6} alkyl, such as methyl, ethyl or t-butyl, C_{1-6} alkoxy, such as methoxy, halo such as bromo, chloro, fluoro or iodo, and trifluoromethyl. When R^2 represents monosubstituted phenyl, the substituent is preferably in the 3-position. When R^2 represents disubstituted phenyl, the substituents are preferably in the 3- and 5-positions.

Particularly preferred are compounds wherein R^2 represents 3,5-bis(trifluoromethyl)phenyl.

A particular subgroup of compounds according to the invention is represented by compounds of formula (Ia), and salts and prodrugs thereof:



wherein the dotted line represents an optional covalent bond;

X represents O, S or NR^{14} (where R^{14} is H, C_{1-6} alkyl, optionally substituted phenyl(C_{1-4} alkyl), CO_2R^a or $CONR^aR^b$, where R^a and R^b are as previously defined), preferably S or NH;

Z is as defined for formula (I);

- 8 -

R^1 is as defined for formula (I), preferably H;
 R^{11} and R^{12} each independently represent H,
 C_1 -6alkyl, C_2 -6alkenyl, C_2 -6alkynyl, halo, cyano, nitro,
trifluoromethyl, trimethylsilyl, OR^a , SR^a , SOR^a , NR^aR^b ,
5 NR^aCOR^b , $NR^aCO_2R^b$, CO_2R^a or $CONR^aR^b$, where R^a and R^b are
as previously defined;

each R^{13} may occupy any available carbon atom
of the bicyclic ring system and independently represents
 C_1 -6alkyl, C_2 -6alkenyl, C_2 -6alkynyl, halo, cyano, nitro,
10 trifluoromethyl, trimethylsilyl, OR^a , SR^a , SOR^a , NR^aR^b ,
 NR^aCOR^b , $NR^aCO_2R^b$, CO_2R^a or $CONR^aR^b$, where R^a and R^b are
as previously defined; and

n is 0, 1, 2 or 3, preferably 0.

Preferred are compounds of formula (Ia) wherein
15 the optional covalent bond is present.

A further subgroup of compounds according to
this invention are analogues of the compounds of the
formula (Ia) but wherein NR^1 is replaced by O and 2 is
20 NR^3 .

For use in medicine, the salts of the compounds
of formula (I) will be non-toxic pharmaceutically
acceptable salts. Other salts may, however, be useful in
the preparation of the compounds according to the
invention or of their non-toxic pharmaceutically
25 acceptable salts. Suitable pharmaceutically acceptable
salts of the compounds of this invention include acid
addition salts which may, for example, be formed by
mixing a solution of the compound according to the
invention with a solution of a pharmaceutically
30 acceptable non-toxic acid such as hydrochloric acid,
sulphuric acid, oxalic acid, fumaric acid, p-
toluenesulphonic acid, maleic acid, succinic acid, acetic
acid, citric acid, tartaric acid, carbonic acid or
phosphoric acid. Salts of amine groups may also comprise

- 9 -

quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible in vivo into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The compounds according to the invention may exist both as enantiomers and as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The substance P antagonising activity of the compounds described herein was evaluated using the human NK1R assay described in published European patent application no. 0 528 495. The method essentially involves determining the concentration of the test compound required to reduce by 50% the amount of radiolabelled substance P binding to human NK1R, thereby affording an IC_{50} value for the test compound. The compounds of the Examples were found to have IC_{50} values of less than 500nM.

The invention also provides pharmaceutical compositions comprising one or more compounds of this

- 10 -

invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or
5 suppositories, for oral, parenteral or rectal administration, or topical administration including administration by inhalation or insufflation.

The invention further provides a process for the preparation of a pharmaceutical composition
10 comprising a compound of formula (I), or a salt or prodrug thereof, and a pharmaceutically acceptable carrier, which process comprises bringing a compound of formula (I), or a salt or prodrug thereof into association with a pharmaceutically acceptable carrier.

15 For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium
20 stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When
25 referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and
30 capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise

- 11 -

compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be

- 12 -

nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine.

- 5 Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

For topical administration, for example as a cream, ointment or lotion, pharmaceutically acceptable
10 carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or arylalkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone, isopropyl
15 myristate and other conventionally-employed non-toxic, pharmaceutically acceptable organic and inorganic carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents
20 and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious
25 in use, thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol, buffering ingredients such as sodium chloride, sodium borate, sodium acetates, gluconate buffers, and other conventional ingredients such as sorbitan monolaurate, triethanolamine, oleate,
30 polyoxyethylene sorbitan monopalmitate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetraacetic acid, and the like.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions

- 13 -

which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. These may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease) and other neuropathological disorders such as peripheral neuropathy, for example, diabetic or chemotherapy-induced neuropathy, and postherpetic and other neuralgias; small cell carcinoma such as small cell lung cancer; respiratory diseases such as chronic obstructive airways disease, bronchopneumonia, bronchospasm and asthma; inflammatory diseases such as inflammatory bowel disease, irritable bowel syndrome, psoriasis, fibrositis, osteoarthritis and rheumatoid arthritis; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like, and proliferative vitreoretinopathy; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis; oedema, such as oedema caused by thermal injury; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and incontinence;

- 14 -

emesis, including acute, delayed and anticipatory emesis, for example, induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, surgery, migraine and variations in intracranial pressure; disorders of bladder
5 function such as cystitis and bladder detrusor hyper-reflexia; fibrosing and collagen diseases such as scleroderma and eosinophilic fasciitis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease;
10 and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

The compounds of formula (I) are particularly useful in the treatment of pain or nociception and/or
15 inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis, post operative pain and especially migraine.

20 The present invention further provides a compound of formula (I) for use in therapy.

According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the
25 treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

The present invention also provides a method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises
30 administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

- 15 -

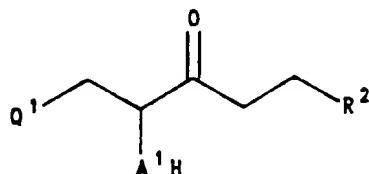
For the treatment of certain conditions it may be desirable to employ a compound according to the present invention in conjunction with another pharmacologically active agent. For example, for the treatment of respiratory diseases such as asthma, a compound of formula (I) may be used in conjunction with a bronchodilator, such as a β_2 -adrenergic receptor antagonist or tachykinin antagonist which acts at NK-2 receptors. The compound of formula (I) and the bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

The present invention accordingly provides a method for the treatment of a respiratory disease, such as asthma, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula (I) and an effective amount of a bronchodilator.

The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day. For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

Compounds of formula (I) wherein A^2 is NR^3 , R^3 is other than H and the double bond is present, may be prepared from intermediates of formula (II):



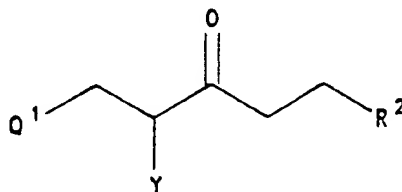
(II)

wherein A^1 is O or NR^1 and Q^1 , R^1 and R^2 are as defined for formula (I), by reaction with an isocyanate of formula R^3NCO where R^3 is as defined for formula (I), other than H, in the presence of a base.

15 Suitable bases of use in the reaction include organic bases, such as a tertiary amine, e.g. triethylamine, and inorganic bases, such as an alkali metal hydride, e.g. sodium hydride.

20 Compounds of formula (I) wherein A^2 is NH and the double bond is present may be prepared by reaction of an intermediate of formula (II) with an isocyanate of formula R^{20}_3SiNCO , where R^{20} is alkyl, such as methyl, in the presence of a base, as previously described.

25 Compounds of formula (I) wherein Z is O and the double bond is present may be prepared by treatment of a compound of formula (III)

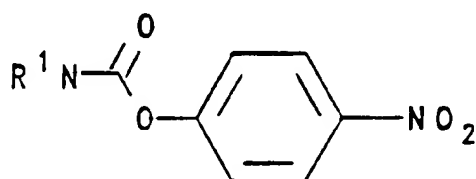


(III)

- 17 -

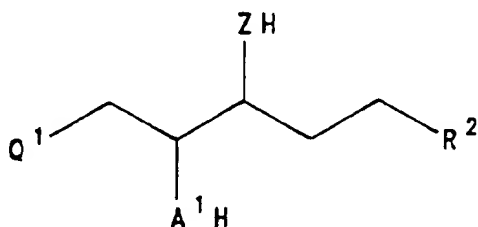
wherein Q^1 and R^2 are as defined for formula (I), and Y represents an activated carbamate, with a base, such as an alkali metal hydride, e.g. sodium hydride.

Suitably Y may represent an appropriately substituted aryl carbamate, e.g.



The reaction is conveniently effected in a suitable organic solvent, such as, for example, dimethyl formamide.

Compounds of formula (I) wherein the double bond is absent may be prepared from compounds of formula (IV)



(IV)

wherein A^1 is O or NR^1 and Q^1 , Z, R^1 and R^2 are as defined for formula (I), by reaction with phosgene or a "phosgene equivalent" such as carbonyl diimidazole, a dialkyl carbonate or an alkylchloroformate, preferably with carbonyl diimidazole.

- 18 -

The reaction may be effected under basic conditions. Suitable bases include, for example, tertiary amines such as triethylamine.

5 The reaction is conveniently effected in a suitable organic solvent such as an ether, e.g. tetrahydrofuran, or a halogenated hydrocarbon, e.g. dichloromethane, suitably at room temperature.

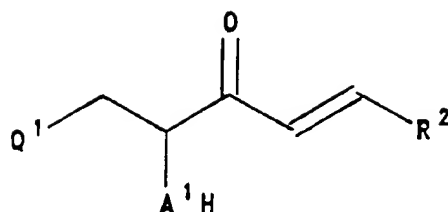
Compounds of formula (I) may also be prepared from other compounds of formula (I). Thus, for example, 10 compounds of formula (I) wherein the double bond is absent may in general be prepared from the corresponding compounds of formula (I) wherein the double bond is present, by reduction. Suitable reduction methods include, for example, hydrogenation in the presence of a 15 catalyst, such as a noble metal catalyst, e.g. palladium, which may be supported, e.g. on carbon. Compounds of formula (I) wherein R^1 and/or R^3 is other than H may be prepared from compounds of formula (I) wherein R^1 and/or R^3 represent H, by conventional procedures, for example 20 alkylation.

Suitable alkylating agents and procedures will be readily apparent to those skilled in the art and include, but are not limited to, reaction with a suitable optionally substituted alkyl halide in the presence of a 25 base, such as an alkali metal hydride, e.g. sodium hydride.

Compounds of formula (II) may be prepared from intermediates of formula (V):

30

- 19 -



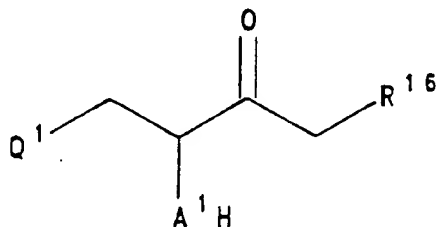
(V)

- 10 wherein A^1 is O or NR^1 and Q^1 , R^1 and R^2 are as defined for formula (I), by reduction.

Suitable reduction procedures include catalytic hydrogenation. Suitable hydrogenation catalysts include nobel metals, for example, platinum or palladium, or
 15 oxides thereof, which may be supported, for example, on charcoal.

The reaction is conveniently effected in a suitable organic solvent, such as an ether, e.g. tetrahydrofuran, an alcohol, e.g. ethanol, or an ester,
 20 e.g. ethyl acetate, suitably at ambient temperature.

Intermediates of formula (V) may be prepared by reaction of an aldehyde of formula R^2CHO with a compound of formula (VI):



(VI)

wherein A^1 is O or NR^1 and Q^1 and R^1 are as defined for formula (I) and R^{16} represents a group PR^X_3 or $PO(OR^X)_2$,

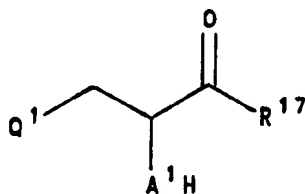
- 20 -

wherein R^X represents phenyl or C_{1-10} alkyl, in the presence of a base.

Suitable bases include alkali metal hydrides, such as, for example, sodium hydride, and strong organic
5 bases such as, for example, 1,8-diazabicyclo[5.4.0] undec-7-ene in the presence of anhydrous lithium chloride.

The reaction is conveniently effected in a suitable organic solvent, such as an ether, e.g. tetrahydrofuran, suitably at ambient temperature.

10 Compounds of formula (VI) may be prepared from compounds of formula (VII):



(VII)

20 wherein A^1 is O or NR^1 and Q^1 and R^1 are as defined for formula (I) and R^{17} represents an alkoxy or a suitably substituted amino group, such as a group NR^YOR^Z , where R^Y and R^Z represent alkyl, in particular a group $\text{NCH}_3(\text{OCH}_3)$,
25 by reaction with a compound of formula $\text{CH}_3\text{PO}(\text{OR}^X)_2$, where R^X is an alkyl group, in the presence of a base.

Suitable reaction procedures will be readily apparent to the skilled person and examples thereof are described in the accompanying Examples.

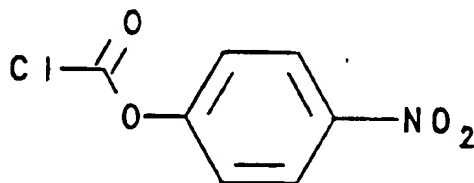
30 Suitable bases of use in the reaction include alkyl lithiums, such as butyl lithiums.

Compounds of formula (VII) are commercially available or may be prepared using standard procedures well known to the person skilled in the art. The compounds of formula (VII) where A^1 is NR^1 are amino acid

- 21 -

derivatives. Syntheses of amino acids and derivatives thereof are well documented and are described, for example, in Chemistry and Biochemistry of the Amino Acids, ed. G. C. Barrett, Chapman and Hall, 1985.

5 Compounds of formula (III) may be prepared from compounds of formula (II) by reaction with a suitable chloroformate, for example



in the presence of a base, such as a tertiary amine, for example, triethylamine.

20 Compounds of formula (IV) wherein Z is O may be prepared from compounds of formula (II) by reduction. Suitable reducing agents include, for example, hydride reducing agents such as, for example, sodium borohydride.

25 Compounds of formula (IV) wherein Z is S may be prepared from the corresponding compounds of formula (IV) wherein Z is O by treatment with Lawesson's reagent or phosphorous pentasulphide in a suitable solvent, e.g. pyridine, at ambient or elevated temperature.

30 Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated, suitably by conventional techniques such as preparative chromatography.

The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by

- 22 -

enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

Using the methods described in PCT/GB92/01212 (International Publication No. WO 93/01159), pages 30-33, it was found that the compounds of the Examples referred to hereinafter had IC₅₀ at NKIR of less than 500nM.

The following non-limiting Examples illustrate the preparation of compounds according to the invention.

- 23 -

EXAMPLE 11-Methyl-4-(indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)phenethyl)imidazolin-2-one

5

(a) N-Methoxy-N-methyl 2-t-butyloxycarbonylamino-3-(3-indolyl)propionamide

10 N- α -BOC-L-tryptophan (100g) was dissolved in dimethyl formamide (800ml) and triethylamine (101g) was added. The reaction was cooled to -30°C and isobutyl chloroformate (42.5ml) was added, maintaining the internal temperature to below -20°C. The reaction was stirred for 15 minutes before adding

15 N,O-dimethyl hydroxylamine hydrochloride (64g) and then diluting the reaction with dichloromethane (1l), maintaining the internal temperature below 0°C. The reaction was stirred for 15 minutes, poured into ethyl acetate (3l) and washed with 10% citric acid (1l), water (3 x 1l), saturated sodium bicarbonate (1l) and water (1l). The organic phase was dried (MgSO₄), filtered,

20 and evaporated until crystallisation ensued. The suspension was diluted with petroleum ether, filtered and dried to yield the title compound; mp 129-130°C; ¹H NMR (360MHz, D₆ DMSO) δ 10.80 (1H, s); 7.51 (1H, d, J = 7Hz); 7.33 (1H, d, J = 7Hz); 7.16 (1H, s); 7.08-6.97 (3H, m); 4.62-4.58 (1H, m); 3.72 (3H, s); 3.34

25 (3H, s); 3.02-2.81 (2H, m); 1.31 (9H, s).

(b) 2-t-Butyloxycarbonylamino-1-(3-indolyl)-4-dimethylphosphono-3-butanone

30

Dimethyl methane phosphonate (205g) was dissolved in tetrahydrofuran (800ml), cooled to -70°C; and then treated with n-butyllithium (1.6M in hexane, 900ml), maintaining the

- 24 -

internal temperature of the reaction at below -55°C. The reaction was stirred for one hour before adding the product of part (a) (90g). The reaction was stirred at -70°C for 30 minutes before quenching with saturated ammonium chloride. The resulting mixture was extracted with ethyl acetate and the organic extract was washed with water (5 x 500ml), dried (MgSO₄) and evaporated. The residue was purified on silica (eluting with ethyl acetate) to yield the title compound as an oil; ¹H NMR (360MHz, CDCl₃) δ 10.84 (1H, s), 7.56 (1H, d, J = 7Hz), 7.33 (1H, d, J = 7Hz), 6.98 (1H, t, J = 7Hz), 4.34-4.31 (1H, m), 3.63 (6H, d, J = 11Hz), 3.39 (2H, d, J = 22Hz), 3.19-3.11 (1H, m), 2.91-2.84 (1H, m); found: C, 55.73, H, 6.34; N, 6.80; C₁₉H₂₇N₂O₆P requires C, 55.60; H, 6.63; N, 6.82%.

15 (c) 5-(3,5-Bis(trifluoromethyl)phenyl)-2-t-butylloxycarbonylamino-1-(3-indolyl)-4-penten-3-one

A solution of the product of part (b) (69.0g) in acetonitrile (600ml) was stirred with diisopropylethylamine (43.3g), and anhydrous lithium chloride (14.13g) for 30 minutes before adding 3,5-bistrifluoromethylbenzaldehyde (55g) in acetonitrile (200ml). The reaction was stirred for two hours then the solvent was removed and the residue partitioned between ethyl acetate and water. The organic phase was washed with 10% citric acid (500ml), water (500ml), saturated sodium bicarbonate (500ml) and water (500ml). The solution was dried (MgSO₄), filtered and evaporated. The residue was purified by column chromatography on silica using ethyl acetate/petroleum ether (1:4) to yield the title compound as a pale yellow solid, mp 137-138°C; found: C, 59.23; H, 4.79; N, 5.35; C₂₆H₂₄F₆N₂O₃ requires C, 59.32; H, 4.60; N 5.32%.

- 25 -

(d) 5-(3,5-Bis(trifluoromethyl)phenyl)-2-t-butylloxycarbonylamino-1-(3-indolyl)-3-pentanone

5 The product of part (c) was heated under reflux with tri-*n*-butyltin hydride (51.12g) in toluene for 20 hours. The reaction was cooled and purified by column chromatography on silica using ethyl acetate/petroleum ether (1:4) to yield the title compound as a white solid (37.1g), mp 138-140°C: found: C, 59.23; H, 4.90; N, 5.28; C₂₆H₂₄F₆N₂O₃ requires C, 59.09, H, 4.96; 10 N, 5.30%.

(e)
2-Amino-5-(3,5-bis(trifluoromethyl)phenyl)-1-(3-indolyl)-3-pentanone Hydrochloride

15 The product of part (d) was treated with ethereal hydrogen chloride for one hour. The precipitated white solid was filtered and dried, mp 84-86°C; found: C, 54.40; H, 4.25; N, 6.10; C₂₁H₁₈F₆N₂O. HCl requires C, 54.26; H, 4.12; N, 6.03%.

20 (f) 1-Methyl-4-(indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)phenethyl)imidazolin-2-one

To a stirred suspension of the compound of part 1(e) (475mg) in dichloromethane (15ml) was added methyl isocyanate (0.15ml) and triethylamine (0.5ml). After 1.5 hours the reaction was washed with dilute hydrochloric acid, then aqueous sodium bicarbonate, dried (Na₂SO₄) and concentrated. Crystallisation from ethyl acetate/diethyl ether gave the title compound, mp 25 191°C; Found: C, 58.07; H, 3.99; N, 8.84. C₂₃H₁₉F₆N₃O.0.5H₂O requires C, 57.99; H, 4.23; N, 8.82.

30

- 26 -

EXAMPLE 24-(3.5-Bis(trifluoromethyl)phenethyl)-5-(indol-3-ylmethyl)
imidazolin-2-one

5 Prepared by the method of Example 1(f) using
trimethylsilylisocyanate and obtained as white crystals, mp
194-195°C; found: C, 57.66; H, 3.72; N, 9.16.
C₂₂H₁₇F₆N₃O.0.25H₂O requires C, 57.71; H, 3.85; N, 9.18.

10

EXAMPLE 34-(Indol-3-ylmethyl)-5-(3.5-bis(trifluoromethyl)phenethyl)
oxazolin-2-one

15

(a) 2-(4-Nitrophenoxycarbonylamino)-5-(3.5-
bis(trifluoromethyl)phenyl)-1-(3-indolyl)-3-pentanone

20 The compound of Example 1(e) (1g) in tetrahydrofuran
(10ml) was treated with bis-(4-nitrophenyl)carbonate (0.66g) and
triethylamine (0.3ml). After stirring for 24 hours the reaction
was diluted with ethyl acetate, washed with water, dried
(Na₂SO₄) and concentrated. Crystallisation from ethyl
acetate-petroleum ether gave the title compound as a white solid.

25

(b) 4-(Indol-3-ylmethyl)-5-(3.5-bis(trifluoromethyl)phenethyl)
oxazolin-2-one

30 A solution of the product of Example 3(a) (300mg) in
dimethylformamide (5ml) was treated with sodium hydride

- 27 -

(20mg of a 60% dispersion in oil) for 16 hours. The reaction was diluted with ethyl acetate, washed with water, dried (NaSO_4) and concentrated. The residue was purified by chromatography on silica gel eluting with ethyl acetate-petroleum ether to give the title compound which was recrystallised from ethyl acetate-petroleum ether, mp 178-180°C; found: C, 58.01; H, 3.75; N, 6.11. $\text{C}_{22}\text{H}_{16}\text{F}_6\text{N}_2\text{O}_2$ requires C, 58.16; H, 3.55; N, 6.16.

EXAMPLE 4

10

4-(Indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)phenethyl)oxazolidin-2-one

15

(a) 5-(3,5-Bis(trifluoromethyl)phenyl)-2-tert-butoxycarbonylamino-1-(1-tert-butoxycarbonylindol-3-yl)-3-pentanone

20

The product of Example 1(d) (6.7g) in dichloromethane (200ml) was treated with di-tertbutyl dicarbonate (2.75g) and N,N-dimethylaminopyridine (1.5g) for 2 hours. The reaction mixture was washed with aqueous citric acid, sodium bicarbonate solution and water then dried (Na_2SO_4) and concentrated to give an oil which was purified by chromatography on silica gel. A sample of the product thus obtained (2g) was dissolved in methanol and treated with sodium borohydride (120mg) for 1 hour. The solvent was evaporated and the residue partitioned between ethyl acetate and water. The organic solution was separated, dried and concentrated to give a residue which was purified by chromatography on silica to give the title compound as two separate diastereomers, isomer A and isomer B.

30

- 28 -

(b) 4-(Indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)phenethyl)
oxazolidin-2-one

5 The compound of Example 4(a), isomer A (70mg), was
dissolved in ethereal hydrogen chloride for 1 hour. The mixture
was concentrated and the residue dissolved in dichloromethane
(5ml) to which was added triethylamine (0.5ml) and carbonyl
diimidazole (100mg). After stirring for 1 hour the reaction was
10 diluted with ethyl acetate, washed with dilute hydrochloric acid
then sodium bicarbonate solution, dried and concentrated.
Chromatography on silica gel eluting with ethyl
acetate-petroleum ether (1:3) gave the title compound, isomer A,
mp 196-198°C; found: C, 55.80; H, 4.02; N, 5.96. $C_{22}H_{20}F_6N_2O_3$
requires C, 55.70; H, 4.25; N, 5.91.

15

In a similar manner the compound of Example 4(a),
isomer B, gave the title compound, isomer B.

EXAMPLE 5

20

1-Ethyl-4-(indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)
phenethyl) imidazolin-2-one

25 To a stirred suspension of the compound of Example 1(e)
(468mg) in dichloromethane (15ml) was added ethyl isocyanate
(0.5ml) and triethylamine (1ml). After 1 hour the solution was
washed with dilute hydrochloric acid, aqueous sodium
bicarbonate, dried (Na_2SO_4) and concentrated. The residue was
dissolved in methanol 5ml and treated with sodium methoxide
30 (0.4g) for 1.5 hours after which time the solution was diluted
with dichloromethane, washed with water, dried and
concentrated. Crystallisation from diethyl ether gave the title

- 29 -

compound, mp 228-230°C; found: C, 59.15; H, 4.42; N, 8.55.
C₂₄H₂₁F₆N₃O.0.25H₂O requires C, 59.32; H, 4.46; N, 8.65.

EXAMPLE 6

5

1-(4-Pyridylmethyl)-4-(indol-3-ylmethyl)-5-(3.5-
bis(trifluoromethyl)phenethyl)imidazolin-2-one

10 a) 5-(3.5-Bis(trifluoromethyl)phenyl)-1-(3-indolyl)-2-(4-
pyridylmethylureido)-3-pentanone Hydrochloride

The compound of Example 1(e) (400mg) in tetrahydrofuran (10ml) was treated with triethylamine (0.12ml) and 4-nitrophenylchloroformate (174mg) for 1 hour. The solvent was removed in vacuo and the residue partitioned between ethyl acetate and water. The organic solution was dried (Na₂SO₄) and concentrated to give a solid which was dissolved in tetrahydrofuran (15ml). 4-Aminomethylpyridine (0.085ml) was added and the solution stirred for 16 hours then concentrated in vacuo. The residue was partitioned between ethyl acetate and potassium carbonate solution. The organic solution was dried (Na₂SO₄), concentrated and the residue treated with ethereal hydrogen chloride to give the title compound, mp 171-174°C; found: C, 53.94; H, 4.31; N, 8.87%. C₂₇H₂₅F₆N₄O₂.HCl.1.5H₂O requires C, 53.72; H, 4.50; N, 8.95%.

25

b) 1-(4-Pyridylmethyl)-4-(indol-3-ylmethyl)-5-(3.5-
bis(trifluoromethyl)phenethyl)imidazolin-2-one

30 The compound of part 7(a) (0.1g) in methanol (5ml) was treated with sodium methoxide (225mg) for 16 hours, then diluted with ethyl acetate, washed with water, dried and concentrated. Crystallisation of the residue from ethyl

- 30 -

acetate-petroleum ether gave the title compound, mp 222-224°C;
found: C, 61.61; H, 4.31; N, 10.07. $C_{28}H_{22}F_6N_4O$ requires C,
61.76; H, 4.07; N, 10.29.

5

EXAMPLE 7

1-Dimethylaminoethyl-4-(indol-3-ylmethyl)-5-(3,5-
bis(trifluoromethyl)phenethyl)imidazolin-2-one

10

Prepared by the method of Example 6 using
2-N,N-dimethylaminoethylamine. Mp 189-191°C; found:
C, 58.73; H, 4.82; N, 10.40. $C_{26}H_{26}F_6N_4O \cdot 0.3H_2O$ requires
C, 58.93; H, 5.05; N, 10.52.

15

EXAMPLE 8

1-Methyl-3-methyl-4-(indol-3-ylmethyl)-5-(3,5-
bis(trifluoromethyl)phenethyl)imidazolin-2-one

20

The compound of Example 1 (0.5g) in tetrahydrofuran (5ml)
was treated with sodium hydride (43mg of a 60% dispersion in oil)
under a nitrogen atmosphere with stirring. After 5 minutes methyl
iodide (0.28g) was added and stirring continued for 2 hours. The
reaction was diluted with ethyl acetate, washed with water, dried
and concentrated. The residue was purified by chromatography on
silica gel eluting with ethyl acetate-petroleum ether and
crystallised from ethyl acetate-petroleum ether to give the title
compound, mp 202-205°C; found: C, 59.88; H, 4.23; N, 8.42.
 $C_{24}H_{21}F_6N_3O$ requires C, 59.88; H, 4.40; N, 8.73.

30

- 31 -

EXAMPLE 91-Dimethylaminopropyl-4-(indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)phenethyl)imidazolin-2-one

5

Prepared by the method of Example 6 using 3-N,N-dimethylaminopropylamine. Mp. 209-211°C; found: C, 60.15; H, 5.30; N, 10.28. $C_{27}H_{28}F_6N_4O$ requires C, 60.22; H, 5.24; N, 10.40.

10

EXAMPLE 101-(4-Piperidinyl)-4-(indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)phenethyl)imidazolin-2-one

15

N-^tButoxycarbonylisonipecotic acid (458mg) in dichloromethane (10ml) was treated with triethylamine (0.28ml) and diphenylphosphoryl azide (0.43ml) for 16 hours. The solvent was removed under reduced pressure and the residue redissolved in dichloromethane (15ml) to which was added triethylamine (0.2ml) and the compound of Example 1(e). After stirring for 6 hours the solvent was evaporated and the residue partitioned between water and ethyl acetate. The ethyl acetate solution was separated, dried (Na_2SO_4) and concentrated to give a residue which was purified by chromatography on silica gel eluting with ethyl acetate-petroleum ether (1:1). The resulting oil was dissolved in ethereal hydrogen chloride for 2 hours. The solution was washed with sodium bicarbonate solution, dried (Na_2SO_4) and evaporated to give the title compound, mp 190°C (decomp.); found: C, 57.71; H, 4.78; N, 9.67. $C_{27}H_{26}F_6N_4O \cdot 1.5H_2O$ requires C, 57.55; H, 5.18; N, 9.94.

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- 32 -

EXAMPLE 11

1-(2-(N-Morpholinyl)ethyl)-4-(indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)phenethyl)imidazolin-2-one

5

Prepared by the method of Example 6 using N-(aminoethyl) morpholine. Mp 207°C; found: C, 59.52; H, 5.13; N, 9.60. $C_{28}H_{28}F_6N_4O_2$ requires C, 59.36; H, 4.98; N, 9.89.

10

EXAMPLE 12

1-(4-Piperidinylmethyl)-4-(indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)phenethyl)imidazolin-2-one Hydrochloride

15

The compound of Example 1(e) was treated with 4-nitrophenylchloroformate and N-Boc-4-aminomethylpiperidine (Synthetic Communications (1992), 22, 2357) by the method of Example 6. After the reaction had stirred for 16 hours dichloromethane was added and the solution washed with water, dried and concentrated. The residue was purified by chromatography on silica gel eluting with ethyl acetate-petroleum ether to give a solid which was dissolved in ethereal hydrogen chloride for 16 hours. The solvent was removed *in vacuo* and the residue crystallised from propan-2-ol/di-isopropyl ether to give the title compound, mp 250°C (decomp.); found: C, 57.28; H, 4.63; N, 9.34. $C_{28}H_{28}F_6N_4O.HCl$ requires C, 57.29; H, 4.98; N, 9.54.

20

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- 33 -

EXAMPLE 134-(3,5-Bis(trifluoromethyl)phenethyl)-5-(indol-3-ylmethyl)-
3-methyloxazolin-2-one

5

(a) N-Methoxy-N-methyl-2-t-butyl dimethylsilyloxy-3-(3-indolyl)propionamide

Indole lactic acid (5.0g) was suspended in dichloromethane (100ml) and treated with triethylamine (6.8ml) and t-butyl dimethylsilyl triflate (5.7ml) for 24 hours. iso-Butyl chloroformate (3.1ml) was added followed by N,O-dimethylhydroxylamine (2.4g) and triethylamine (3.4ml). The solution was stirred for 24 hours then washed with water, dried (Na₂SO₄) and concentrated. The residue was purified by chromatography on silica gel eluting with ethyl acetate-petroleum ether to give the title compound as a white solid.

15

(b) 5-(3,5-Bis(trifluoromethyl)phenyl)-2-t-butyl dimethylsilyloxy-1-(3-indolyl)-4-penten-3-one

Prepared from the compound of Example 13(a) by the methods of Examples 1(b) and 1(c).

20

(c) 5-(3,5-Bis(trifluoromethyl)phenyl)-2-hydroxy-1-(3-indolyl)-3-pentanone

The compound of Example 13(b) in ethyl acetate was shaken under an atmosphere of hydrogen gas at 50psi over 10% Pd-C for 24 hours. The mixture was filtered, concentrated and dissolved in tetrahydrofuran containing tetrabutylammonium fluoride for 3 hours. The solution was diluted with water and extracted with diethyl ether which was then dried and concentrated to give a residue which was purified on silica gel eluting with ethyl acetate-petroleum ether (2:3). Crystallisation from diethyl ether-petroleum ether gave the title compound as a white solid.

25

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- 34 -

(d) 4-(3,5-Bis(trifluoromethyl)phenethyl)-5-(indol-3-ylmethyl)-3-methyloxazolin-2-one

5 The compound of Example 13(c) (0.15g) was dissolved in methyl isocyanate (1ml). After 6 hours the solution was concentrated *in vacuo* and the residue dissolved in methanol (2ml) containing sodium methoxide for 30 minutes. The solution was diluted with diethyl ether and washed with 5N hydrochloric acid, dried and concentrated. The residue was purified on silica gel eluting with ethyl acetate-hexane (2:3) to give the title compound as a white solid, mp 109-110 °C;
10 found: C, 59.22; H, 3.86; N, 5.70. $C_{23}H_{18}F_6N_2O_2$ requires C, 58.98; H, 3.87; N, 5.98.

- 35 -

The following examples illustrate pharmaceutical compositions according to the invention.

EXAMPLE 14A Tablets containing 1-25mg of compound

5		<u>Amount mg</u>		
	Compound of formula (I)	1.0	2.0	25.0
	Microcrystalline cellulose	20.0	20.0	20.0
	Modified food corn starch	20.0	20.0	20.0
	Lactose	58.5	57.5	34.5
10	Magnesium Stearate	0.5	0.5	0.5

EXAMPLE 14B Tablets containing 26-100mg of compound

		<u>Amount mg</u>		
	Compound of formula (I)	26.0	50.0	100.0
15	Microcrystalline cellulose	80.0	80.0	80.0
	Modified food corn starch	80.0	80.0	80.0
	Lactose	213.5	189.5	139.5
	Magnesium Stearate	0.5	0.5	0.5
20	The compound of formula (I), cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing			
25	1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active compound per tablet.			

EXAMPLE 15 Parenteral injection

		<u>Amount mg</u>
30	Compound of formula (I)	1 to 100mg
	Citric Acid Monohydrate	0.75mg
	Sodium Phosphate	4.5mg
	Sodium Chloride	9mg
	Water for Injections	to 1ml

- 36 -

The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The compound of formula (I) is dissolved or suspended in the solution and made up to volume.

5

EXAMPLE 16 Topical formulation

	<u>Amount mg</u>
Compound of formula (I)	1-10g
Emulsifying Wax	30g
10 Liquid paraffin	20g
White Soft Paraffin	to 100g

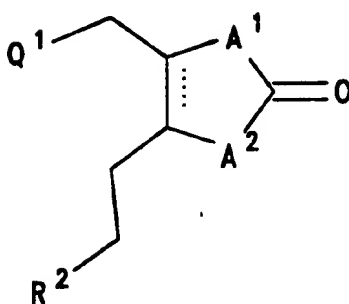
The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The compound of formula (I) is added and stirring continued until dispersed. The mixture is then cooled until solid.

15

- 37 -

CLAIMS:

1. A compound of formula (I), or a salt or
 5 prodrug thereof:



(I)

wherein

Q¹ represents a phenyl group substituted by one or more halo, optionally substituted naphthyl, optionally substituted indolyl, optionally substituted
 20 benzthiophenyl, optionally substituted benzofuranyl, optionally substituted benzyl or optionally substituted fluorenyl;

the dotted line represents an optional covalent bond;

25 one of A¹ and A² represents NR¹ and the other is Z where Z represents O or NR³;

R¹ and R³ each independently represent H;

C₁-₆alkyl optionally substituted by hydroxy, cyano, CORᶜ, CO₂Rᶜ, CONRᶜRᵈ, or NRᶜRᵈ (where Rᶜ and Rᵈ each
 30 independently represent H, C₁-₆alkyl or C₀-₄alkylphenyl optionally substituted in the phenyl ring by one or more of C₁-₆alkyl, C₁-₆alkoxy, halo or trifluoromethylmethyl); phenyl(C₁-₄alkyl) (optionally substituted in the phenyl ring by one or more of C₁-₆alkyl, C₁-₆alkoxy, halo and

- 38 -

trifluoromethyl); COR^{C} ; $\text{CO}_2\text{R}^{\text{C}}$; $\text{CONR}^{\text{C}}\text{R}^{\text{d}}$; $\text{COC}_{1-4}\text{alkylNR}^{\text{C}}\text{R}^{\text{d}}$; $\text{CONR}^{\text{C}}\text{COOR}^{\text{d}}$; $\text{SO}_2\text{R}^{\text{C}}$, where R^{C} and R^{d} are as above defined; WR^6 or CO-Y-W-R^6 where R^6 is an optionally substituted aromatic or non-aromatic azacyclic or azabicyclic group,
5 Y is a bond, O, S or NR^{Y} , where R^{Y} is H or $\text{C}_{1-6}\text{alkyl}$, and W represents a bond or a saturated or unsaturated hydrocarbon chain of 1, 2, 3, 4, 5 or 6 carbon atoms;

R^2 represents phenyl optionally substituted by 1, 2, or 3 groups selected from $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$,
10 $\text{C}_{2-6}\text{alkynyl}$, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, OR^{a} , SR^{a} , SOR^{a} , $\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $\text{NR}^{\text{a}}\text{COR}^{\text{b}}$, $\text{NR}^{\text{a}}\text{CO}_2\text{R}^{\text{b}}$, $\text{CO}_2\text{R}^{\text{a}}$ or $\text{CONR}^{\text{a}}\text{R}^{\text{b}}$, where R^{a} and R^{b} independently represent H, $\text{C}_{1-6}\text{alkyl}$, phenyl or trifluoromethyl.

15 2. A compound as claimed in claim 1 wherein R^1 and R^3 each independently represent H; $\text{C}_{1-6}\text{alkyl}$ optionally substituted by hydroxy, cyano, COR^{C} , $\text{CO}_2\text{R}^{\text{C}}$, $\text{CONR}^{\text{C}}\text{R}^{\text{d}}$, or $\text{NR}^{\text{C}}\text{R}^{\text{d}}$; phenyl($\text{C}_{1-4}\text{alkyl}$) (optionally substituted in the phenyl ring by one or more of
20 $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkoxy}$, halo and trifluoromethyl); COR^{C} ; $\text{CO}_2\text{R}^{\text{C}}$; $\text{CONR}^{\text{C}}\text{R}^{\text{d}}$; $\text{COC}_{1-4}\text{alkylNR}^{\text{C}}\text{R}^{\text{d}}$; $\text{CONR}^{\text{C}}\text{COOR}^{\text{d}}$; $\text{SO}_2\text{R}^{\text{C}}$; $(\text{CH}_2)_q\text{R}^6$ or $\text{CO}(\text{CH}_2)_q\text{R}^6$ where q is 0, 1, 2, 3, 4, 5 or 6.

25 3. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in claim 1 or claim 2 wherein the double bond is present.

4. A compound as claimed in claim 1 or claim 3 wherein Z is NR^3 .

30

5. A compound as claimed in claim 4 wherein R^3 is H or $\text{C}_{1-3}\text{alkyl}$.

- 39 -

6. A compound as claimed in claim 4 wherein R^3 represents C_{1-6} alkyl substituted by $NR^C R^d$ or $Y-W-R^6$.

7. A compound as claimed in any preceding claim wherein A^1 is O.

8. A compound as claimed in any preceding claim wherein R^2 is phenyl substituted by one or more of C_{1-6} alkyl, C_{1-6} alkoxy, halo or trifluoromethyl.

10

9. A compound as claimed in claim 1 selected from:

1-methyl-4-(indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)phenethyl)imidazolin-2-one;
4-(3,5-bis(trifluoromethyl)phenethyl)-5-(indol-3-ylmethyl)imidazolin-2-one;
4-(indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)phenethyl)oxazolin-2-one;
4-(indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)phenethyl)oxazolidin-2-one;
1-ethyl-4-(indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)phenethyl)imidazolin-2-one;
1-(4-pyridylmethyl)-4-(indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)phenethyl)imidazolin-2-one;
1-dimethylaminoethyl-4-(indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)phenethyl)imidazolin-2-one;
1-methyl-3-methyl-4-(indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)phenethyl)imidazolin-2-one;
1-dimethylaminopropyl-4-(indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)phenethyl)imidazolin-2-one;
1-(4-piperidinyl)-4-(indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)phenethyl)imidazolin-2-one;
1-(2-(N-morpholinyl)ethyl)-4-(indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)phenethyl)imidazolin-2-one;

- 40 -

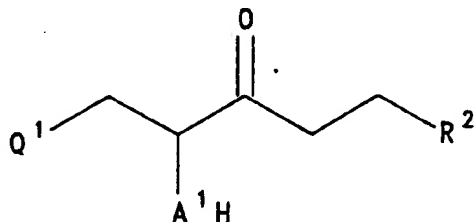
1-(4-piperidinylmethyl)-4-(indol-3-ylmethyl)-5-(3,5-bis(trifluoromethyl)phenethyl)imidazolin-2-one hydrochloride;

4-(3,5-bis(trifluoromethyl)phenethyl)-5-(indol-3-ylmethyl)-3-methyloxazolin-2-one;
 5 and their pharmaceutically acceptable salts and prodrugs thereof.

10 10. A compound as claimed in any preceding claim for use in therapy.

11. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 9 in association with a pharmaceutically acceptable carrier.
 15

12. A process for the preparation of a compound as claimed in claim 1 which process comprises
 (A) reacting an intermediate of formula (II):

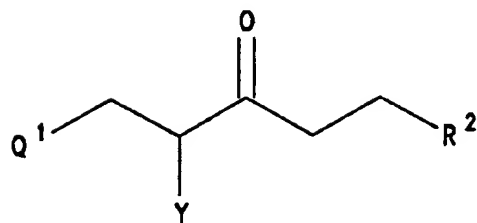


(II)

30 wherein A¹ is O or NR¹ and Q¹, R¹ and R² are as defined for formula (I), with an isocyanate of formula R³NCO, where R³ is as defined for formula (I), other than H, or R²⁰SiNCO, where R²⁰ is alkyl, in the presence of a base; or

- 41 -

(B) treating an intermediate of formula (III):

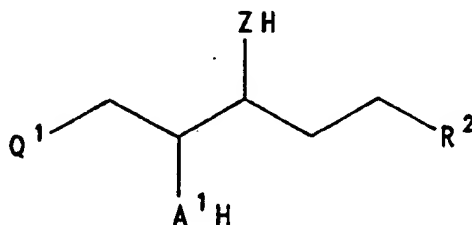


(III)

wherein Q^1 and R^2 are as defined for formula (I) and Y represents an activated carbamate, with a base; or

15

(C) reacting an intermediate of formula (IV):



(IV)

wherein A^1 is O or NR^1 and Q^1 , Z, R^1 and R^3 are as defined for formula (I), with phosgene or a phosgene equivalent.

30

13. A method for the treatment or prevention of a physiological disorder associated with an excess of tachykinins, which method comprises administration to a patient in need thereof of a tachykinin-reducing amount of a compound according to claim 1.

- 42 -

14. A method according to claim 13 for the treatment or prevention of pain or inflammation.

5 15. A method according to claim 13 for the treatment or prevention of migraine.

10 16. A method according to claim 13 for the treatment or prevention of arthritis.

17. The use of a compound as claimed in claim 1 for the manufacture of a medicament for the treatment of a physiological disorder associated with an excess of tachykinins.

15 18. The use of a compound as claimed in claim 1 for the manufacture of a medicament for the treatment of pain or inflammation.

20 19. A compound as claimed in any of claims 1 to 10 when prepared by the process of claim 12.

25 20. A process for preparing a composition as claimed in claim 11 which process comprises bringing a compound as claimed in any of claims 1 to 9 into association with a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 93/02131

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D403/06 C07D405/06 C07D401/14 A61K31/415 A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TETRAHEDRON LETTERS no. 1, 1977 pages 61 - 64 RYMANTAS KAZLAUSKAS ET. AL. *Page 63: formula 11*	1
P,A	EP,A,0 545 478 (MERCK SHARP & DOHME LTD) 9 June 1993 *Document*	1-20



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

2 February 1994

Date of mailing of the international search report

0 8. 02. 94

Name and mailing address of the ISA

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Authorized officer

Luyten, H

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB93/02131

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 13 - 16 are directed to a method of treatment of
(diagnostic method practised on) the human/animal body the search has been
carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such
an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 93/02131

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0545478	09-06-93	CA-A- 2083891	04-06-93
